U.S. DEPARTMENT OF COMMERCE PATENT & TRADEMARK OFFICE

Form PTO-1390 **Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under *35 USC 371***

Attorney's Docket Number	U.S Application Number (if known)
LIGN3005/REF	10/088496

International Application Number	International Filing Date	Priority Date Claimed
PCT/SE00/01923	5 October 2000	7 October 1999

Title of Invention
Use of Xanthophylls, Astaxanthin e.g., for Treatment of Autoimmune Diseases, Chronic Viral and Intracellular Bacterial Infections

Applicant(s) for DO/EO/US
LIGNELL et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items under *35 USC 371*:

1. ☒ This is a **FIRST** submission of items concerning a filing under *35 USC 371*.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under *35 USC 371*.
3. ☒ This express request to begin national examination procedures *(35 USC 371(f))* at any time rather than delay examination until the expiration of the applicable time limit set in *35 USC 371(b)* and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed *35 USC 371(c)(2)*.
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English *(35 USC 371(c)(2))*.
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 *(35 USC 371(c)(3))*.
9. ☒ An oath or declaration of the inventor(s) *(35 USC 371(c)(4))*. (☒ Executed ☐ Unexecuted)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 *(35 USC 371(c)(5))*.

Items 11 to 16 below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under *37 CFR 1.97* and *1.98*.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with *37 CFR 3.28* and *3.31* is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English translation of the international application under 35 U.S.C. 154(d)(4)
20. ☒ Other items or information: Application Data Sheet

Application Number (if Known)	International Application Number	Attorney's Docket Number
10/088496		

	Calculations	PTO USE ONLY
1. The following fees are submitted:		
Basic National Fee *(37 CFR 1.492(a)(1)-(5))*:		
☒ Neither International Preliminary Examination Fee *(37 CFR 1.482)* nor International Search Fee *(37 CFR 1.445(a)(2))* paid to USPTO $1040.00		
☐ Search report has been prepared by the EPO or JPO $890.00		
☐ International Preliminary Examination Fee paid to USPTO *(37 CFR 1.482)* $710.00		
☐ No International Preliminary Examination Fee paid to USPTO *(37 CFR 1.482)* but International Search Fee paid to USPTO *(37 CFR 1.445(a)(2))* $740.00		
☐ International Preliminary Examination Fee paid to USPTO *(37 CFR 1.482)* and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT	$ 1,040.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date *(37 CFR 1.492(e))*.		

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total Claims	17	-20 =	0	× $18.00	$ 0.00	
Independent Claims	2	-3 =	0	× $84.00	$ 0.00	
Multiple Dependent Claims (if applicable)				+ $280.00		

TOTAL OF ABOVE CALCULATIONS	$ 1,040.00	
Reduction by ½ for filing by small entity, if applicable. Small Entity Status is asserted pursuant to 37 CFR 1.27 for this application.		
SUBTOTAL	$ 520.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date *(37 CFR 1.492(f))*.		
TOTAL NATIONAL FEE		
Fee for recording the enclosed assignment *(37 CFR 1.21(h))*. The assignment must be accompanied by an appropriate cover sheet *(37 CFR 3.28, 3.31)*. **$40.00** per property.	$ 40.00	
TOTAL FEES ENCLOSED	$ 560.00	
Amount to be:	Refunded:	
	Charged:	

a. ☒ A check in the amount of **$560.00** to cover the fees is enclosed.

b. ☐ Please charge my **Deposit Account Number 02-0200** in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to **Deposit Account Number 02-0200**. A duplicate copy of this sheet is enclosed.

Note: Where an appropriate time limit under *37 CFR 1.494* or *1.495* has not been met, a petition to revive *(37 CFR 1.137(a) or (b))* must be filed and granted to restore the application to pending status.

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DATE: March 28, 2002

Respectfully submitted,

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Application Data Sheet

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Application Information

Title Line One::	USE OF XANTHOPHYLLS, ASTAXANTHIN E.G.,
Title Line Two::	FOR TREATMENT OF AUTOIMMUNE DISEASES,
Title Line Three::	CHRONIC VIRAL AND INTRACELLULAR
Title Line Four::	BACTERIAL INFECTIONS
Total Drawing Sheets::	0
Formal Drawings?::	N/A
Application Type::	Utility
Docket Number::	LIGN3005/REF

Small Entity Status::	Yes
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Representative Information

Registration Number::	26,382

Continuity Information

This application is a::	371
>Application One::	PCT/SE00/01923
Filing Date::	October 5, 2000

Prior Foreign Applications

Foreign Application One::	9903619-6
Filing Date::	October 7, 1999
Country::	Sweden
Priority Claimed::	Yes

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LIGNELL et al.

U.S. National Phase of PCT/SE00/01923

Entry papers filed herewith March 28, 2002

Attention: PCT OFFICE

For: Use of Xanthophylls, Astaxanthin e.g., for Treatment of Autoimmune Diseases, Chronic Viral and Intracellular Bacterial Infections

PRELIMINARY AMENDMENT
AND INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The present application is the U.S. national phase of international application number PCT/SE00/01923.

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please add the attached ABSTRACT OF THE DISCLOSURE to the application.

IN THE CLAIMS:

Please cancel claims 1-8 without prejudice or disclaimer.

Please replace claim 14 with the following amended claim 14.

14(Amended). The method according to claim 12, wherein the astaxanthin is derived from a natural source.

Please add the following new claims to the application.

16(New). The method according to claim 13, wherein the astaxanthin is derived from a natural source.

17(New). The method according to claim 16, wherein the natural source is a culture of the algae *Haematococcus sp.*

18(New). A medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient which comprises an effective amount of at least one type of xanthophyll for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in said patient.

19(New). A medicament according to claim 18, wherein the excessive Th1 cell mediated immune responses are caused by at least one disease from the group of autoimmune diseases and chronic viral and intracellular bacterial infections.

20(New). A medicament according to claim 18, wherein the disease is Psoriasis vulgaris, Multiple sclerosis (MS), Reumatoid arthritis, Crohn's disease, Insulin-dependent diabetes mellitus, Tubercolosis (TB), Actue graft-versus-host disease (transplant rejection), or HIV virus infection.

21(New). A medicament according to claim 18, wherein the type of xanthophyll is astaxanthin.

22(New). A medicament according to claim 19, wherein the astaxanthin is in a form esterified with fatty acids.

23(New). A medicament according to claim 21, wherein the astaxanthin is derived from a natural source.

24(New). A medicament according to claim 23, wherein the natural source is a culture of the algae *Haematococcus sp*.

25(New). A medicament according to claim 16, wherein the medicament is an oral preparation.

REMARKS

Applicants have amended the claims in order to more particularly define the invention and to reduce the initial filing fee by deleting the multiple dependent claims from the application. The claims have been amended to remove the improper use claims. Applicants retain the right to reintroduce any subject matter canceled by the present Amendment at any time during the prosecution of this application or any further application claiming benefit of this application. Also, an Abstract of the Disclosure has been added to the application.

Applicants are submitting herewith a copy of the Search Report which issued on International Application No. PCT/SE00/01923, of which the present application is the U.S. national phase and was filed and published in English. All of the publications cited in the International Search Report are listed on the attached Form PTO-1449. It is Applicants' understanding that, under the procedures of the PCT, copies of the cited publications will have been supplied to the U.S. Patent Office by the International Bureau. However, the Examiner is invited to contact the undersigned attorney if additional copies are necessary or would facilitate examination of the present application.

Otherwise, the Examiner is respectfully requested to return an initialed and dated copy of the attached Form PTO-1449 to confirm that all publications listed thereon have been considered and made officially of record in the file of this application.

Applicants understand that, under the procedures of the PCT, a copy of the priority document (SE 9903619-6, filed October 7, 1999) will have been supplied to the U.S. Patent Office pursuant to Rule 17 of the PCT Regulations. It is therefore respectfully requested that the first Official Action in the present application contain an indication that the appropriate priority document is in the file of this application.

In view of the above amendments, an early action on the application is now in order and is most respectfully requested.

Respectfully submitted,
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DATE: March 28, 2002

Marked-Up Version Showing Changes Made

IN THE CLAIMS:

14(Amended). The method according to claim 12 [or 13], wherein the astaxanthin is derived from a natural source.

ABSTRACT OF THE DISCLOSURE

The use of at least one type of xanthophylls for the production of a medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient is disclosed. Excessive Th1 cell mediated immune responses are caused by such autoimmune diseases and chronic viral and intracellular bacterial infections as Psoriasis vulgaris, Multiple sclerosis (MS), Rheumatoid arthritis, Crohn's disease, Insulin-dependent diabetes mellitus, Tuberculosis (TB), Acute graft-versus-host disease (transplant rejection) and HIV virus infection. The preferred type of xanthophyll is astaxanthin, particularly in a form esterified with fatty acids, obtainable by for example culturing the algae *Haematococcus sp.* Further, a method of suppressing excessive Th1 mediated immune responses and stimulating Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient is disclosed.

Use of xanthophylls, astaxanthin e.g., for treatment of autoimmune diseases, chronic viral and intracellular bacterial infections.

The present invention relates to the use and method of treatment concerning utilization of xanthophylls, e.g. astaxanthin, for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient.

Background of the invention.

CD4 T lymphocytes can be subdivided into two major subsets - Th1 cells and Th2 cells. These cells release different sets of cytokines that define their distinct actions in immunity. Th1 cells secrete interferon-gamma (IFN-γ) and are mainly involved in activating macrophages and CD8+ cytotoxic T-lymphocytes. Th2 cells secrete the interleukins Il-4, Il-5 and Il-10 and are mainly involved in stimulating B cells to produce antibodies.

There is a balance between the activities of the Th1 and Th2 cells in a normal human body. An excess of Th1 cell activity may be the result of an autoimmune disease, or the result of an ongoing infection. In the normal case, the Th1 cell activity diminishes when the physiological need thereof is reduced. An excess activity is thus seen when the normal reduced level of Th1 cell activity is not achieved as a response to the diminishing presence of the agent that induced the reaction, e.g. the starting point of an autoimmune disease.

Immune modulation aims at altering the balance between different subsets of responding T cells so that damaging responses are suppressed. In many cases autoimmune diseases and intracellular infections are associated with the activation of Th1 cells, which activate macrophages and drive an inflammatory immune response. The drugs currently used to suppress the immune system can be divided into three categories:

1) Powerful anti-inflammatory drugs of the corticosteroid family such as prednisone. Glucocorticoids influence virtually every cellular and humoral mechanism related to inflammation and immune response. However, there are also many adverse effects, including fluid retention, weight gain, diabetes, bone mineral loss and thinning of the skin.

2) Cytotoxic drugs such as azthioprine and cyclophosphamide. Cytotoxic drugs cause immunosuppression by killing dividing cells and they have serious side-effects. The use of these compounds is limited due to a range of toxic effects on tissues that have continuous cell dividing, such as the bone marrow.

3) Cyclosporin A, tacromycin and rapamycin are powerful immunosuppressive agents that interfere with T-cell signaling.

All of these drugs are very broad in their action and inhibit protective functions of the immune system as well as pathological responses that cause tissue injury. Opportunistic infection is therefore a common complication of immune suppressive drugs.

It would be desirable to have an immunosuppressive agent that targets the specific part of the immune response that causes tissue injury. In particular, it would be desirable to obtain a medicament for suppression of harmful, i.e. excessive, Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient.

Description of the invention

The present invention provides a medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient.

One aspect of the invention is directed to the use of at least one type of xanthophylls for the production of a medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient.

In a preferred embodiment of the invention the excessive Th1 cell mediated immune responses are caused by at least one disease from the group of autoimmune diseases and chronic viral and intracellular bacterial infections.

Examples of diseases that cause excessive Th1 cell mediated immune responses are Psoriasis vulgaris, Multiple sclerosis (MS), Reumatoid arthritis, Crohn´s disease, Insulin-dependant diabetes mellitus, Tubercolosis (TB), Acute graft-versus-host disease (transplant rejection) and HIV virus infection.

Xanthophylles, including astaxanthin, is a large group of carotenoids containing oxygen in the molecule in addition to carbon and hydrogen. The carotenoids are produced *de novo* by plants, fungi and some bacteria [Johnson E.A. and Schroeder W.A., 1995, Adv In Biochem Engin. Biotechn. 53: 119-178].

In a preferred embodiment of the invention, the type of xanthophyll is astaxanthin, preferably in a form esterified with fatty acids.

In a particularly preferred embodiment the astaxanthin is derived from a natural source, such as a culture of the algae *Haematococcus sp.*, e.g. *Haemotococcus pluvialis.*

The medicament in the invention is preferably an oral preparation, which optionally comprises an oil of food grade and it is suitably presented in separate unit doses.

The medicament may comprise a mixture of different types of xanthophylls or different forms of the same xanthophyll, such as a mixture of synthetic astaxanthin and naturally produced astaxanthin.

The oral preparation may comprise in addition to the xanthophylls auxiliary ingredients that are pharmacologically acceptable inactive or active ingredients, such as flavoring agents, fillers, emulsifiers, etc.

Examples of separate unit doses are tablets, gelatin capsules and predetermined amounts of solutions, e.g. oil solutions, or emulsions, e.g. water-in- oil or oil-in-water emulsions.

Another aspect of the invention is directed to a method of suppressing excessive Th1 cell mediated immune responses and stimulating Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient comprising administration of an Th1 cell response suppressing and Th2 cell response stimulating amount of at least one type of xanthophylls to said patient.

The examples and preferred embodiments described for the use aspect of the invention also apply for this method aspect of the invention.

In particular, excessive Th1 cell mediated immune responses are caused by at least one disease from the group of autoimmune diseases and chronic viral and intracellular bacterial infections, such as Psoriasis vulgaris, Multiple sclerosis (MS), Reumatoid arthritis, Crohn´s disease, Insulin-dependent diabetes mellitus, Tubercolosis (TB), Acute graft-versus-host disease (transplant rejection) and HIV virus infection, and the type of xanthophyll is preferably astaxanthin, particularly in a form esterified with fatty acids, e.g. from a natural source, such as a culture of the algae *Haematococcus sp.*

The daily doses of the active ingredient of the invention will normally be in the range of 0.01 to 10 mg per kg body weight for a human calculated on the amount of astaxanthin, but the actual dose will depend on the immune response of the individual human patient, the reason for suppression of the excessive Th1 cell mediated immune response, such as the type of disease causing the enhanced pathological Th1 cell response, and the recommendations of the manufacturer.

The xanthophyll astaxanthin is commercially produced via culturing of the algae *Haematococcus sp.* by AstaCarotene AB, Gustavsberg, Sweden. It is marketed and sold in Sweden as a dietary supplement

Astaxanthin from other sources, and other xanthophylls as well, are expected to be similarly useful for the purposes of the invention. An advantage of using astaxanthin from

algae is, however, that the astaxanthin exists in a form esterified with fatty acids [Renström B. et al, 1981, Phytochem 20(11) :2561-2564], which esterified astaxanthin thereby is more stable during handling and storage than free astaxanthin.

The naturally produced astaxanthin can be obtained also from fungi and crustaceans, in addition to from algae [Johnson E.A. and Schroeder W.A., ibid].

Case studies

During the last five years reports have been received from patients taking the commercial dietary supplement capsules of the algal meal of *Haematococcus pluvialis,* Astaxin®, containing 4 mg astaxanthin. The daily doses recommended as an antioxidant is one capsule per day. However, 2 – 6 times that dose has been used by some patients without adverse effects. On the contrary, the higher doses have been experienced as beneficial in alleviating symptoms associated with some chronic diseases.

Six patient histories are disclosed more in detail below.

Chron´s disease

Patient 1. Boy, 17 years old, who had suffered from Crohn´s disease for at least four years. He has been treated with anti-inflammatory agents, such as cortisone. He started to take the commercial product Astaxin (two capsules, each containing 4 mg of astaxanthin, per day). In about two months the cortisone treatment was phased out and later on stopped altogether. The patient was asymptomatic for more than a year when he experienced a relapse. He was then received a short-term treatment with cortisone in combination with Astaxin, and the cortisone treatment was again phased out.

Patient 2. Woman, about 50 years of age, who had suffered from Crohn´s disease for a long time. She received treatment with cortisone. Now she has started to take Astaxin in parallel with her steroid medication and she reports that she feels considerably better.

Patient 3. Man, 48 years old, who has suffered from Crohn´s disease for the last 20 years. He has been operated on several times and he has been treated with cortisone. Directly after the last operation he started taking Astaxin (6 capsules per day) and no cortisone. With regard to the circumstances, he has been asymptomatic. He has compared his clinical status after the operation with the status of two other patients who were operated on at the same time and who received conventional treatment with cortisone. In comparison with these two other patients his recovery has been fully equal with theirs, with the positive exception that edema in his colon diminished more quickly than in the two other patients.

Lichen ruber planus.

Patient 4. Woman, more than 70 years of age, who had suffered from the disease for several years. The symptoms of the disease were *inter alia* open wounds which had not healed. She had been treated with anti-inflammatory agents, such as cortisone, for several years, orally and also by injection directly to the local inflammation areas. The treatment has not led to any result. She started to take 4 capsules of Astaxin per day , and after some weeks visible alleviation of the symptoms started to show up. The wounds were healed in slightly more than one month. During this period, the patient herself phased out the cortisone treatment. The dose of Astaxin was lowered to 2 capsules per day when she was asymtomatic. However, the symptoms returned in connection with a common cold. The dose was then increased to 4 capsules per day and the wounds healed again. She says herself that she now feels considerably better.

Psoriasis.

Patient 5. Male, 40 years, who suffers from psoriasis and mainly shows itself in rough skin on the elbows. After treatment with a skin cream enriched with algal meal/astaxanthin (100 mg astaxanthin /kg cream) twice a day for three weeks, the symptoms diminished.

Patient 6. Woman, 45 years old, who suffers from psoriasis and mainly shows itself in rough skin on the elbows. After treatment with a skin cream enriched with algal meal/astaxanthin (100 mg astaxanthin /kg cream) twice a day for three weeks, the symptoms diminished.

Thus, positive reports have been received from several patients suffering from Crohn´s disease, rheumatoid arthritis, psoriasis and lichen planus. All of these diseases are autoimmune diseases which are known to be Th1 cell mediated diseases.

Therefore it is likely that the Th1 mediated response in the patients has been suppressed and that there is a shift of the Th1/Th2 balance of the immune response towards the Th2 response. Further, it is likely that patients suffering from other predominantly Th1 cell mediated diseases would benefit from suppression of excessive Th1 cell responses and stimulation of Th2 cell mediated immune responses during ongoing infection and/or inflammation.

Claims

1. Use of at least one type of xanthophylls for the production of a medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient.

2. Use according to claim 1, wherein the excessive Th1 cell mediated immune responses are caused by at least one disease from the group of autoimmune diseases and chronic viral and intracellular bacterial infections.

3. Use according to claim 2, wherein the disease is Psoriasis vulgaris, Multiple sclerosis (MS), Reumatoid arthritis, Crohn's disease, Insulin-dependant diabetes mellitus, Tubercolosis (TB), Acute graft-versus-host disease (transplant rejection), or HIV virus infection.

4. Use according to any one of claims 1 -3, wherein the type of xanthophyll is astaxanthin.

5. Use according to claim 4, wherein the astaxanthin is in a form esterified with fatty acids.

6. Use according to claim 4 or 5, wherein the astaxanthin is derived from a natural source.

7. Use according to claim 6, wherein the natural source is a culture of the algae *Haematococcus sp.*

8. Use according to any one of the claims 1 - 7, wherein the medicament is an oral preparation.

9. A method of suppressing excessive Th1 cell mediated immune responses and stimulating Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient comprising administration of an Th1 cell response suppressing and Th2 cell response stimulating amount of at least one type of xanthophylls to said patient.

10. The method according to claim 9, wherein the excessive Th1 cell mediated immune responses are caused by at least one disease from the group of autoimmune diseases and chronic viral and intracellular bacterial infections.

11. The method according to claim 10, wherein the disease is Psoriasis vulgaris, Multiple sclerosis (MS), Reumatoid arthritis, Crohn's disease, Insulin-dependant diabetes mellitus, Tubercolosis (TB), Acute graft-versus-host disease (transplant rejection), or HIV virus infection.

12. The method according to claim 9, wherein the type of xanthophyll is astaxanthin.

13. The method according to claim 12, wherein the astaxanthin is in a form esterified with fatty acids.

14. The method according to claim 12 or 13, wherein the astaxanthin is derived from a natural source.

15. The method according to claim 14, wherein the natural source is a culture of the algae *Haematococcus sp.*

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WO 01/24787 A1

(54) Title: USE OF XANTHOPHYLLS, ASTAXANTHIN E.G., FOR TREATMENT OF AUTOIMMUNE DISEASES, CHRONIC VIRAL AND INTRACELLULAR BACTERIAL INFECTIONS

(57) Abstract: The use of at least one type of xanthophylls for the production of a medicament for suppression of excessive Th1 cell mediated immune responses and stimulation of Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient is disclosed. Excessive Th1 cell mediated immune responses are caused by such autoimmune diseases and chronic viral and intracellular bacterial infections as Psoriasis vulgaris, Multiple sclerosis (MS), Rheumatoid arthritis, Crohn's disease, Insulin-dependent diabetes mellitus, Tuberculosis (TB), Acute graft-versus-host disease (transplant rejection) and HIV virus infection. The preferred type of xanthophyll is astaxanthin, particularly in a form esterified with fatty acids, obtainable by for example culturing the algae *Haematococcus sp.* Further, a method of suppressing excessive Th1 mediated immune responses and stimulating Th2 cell mediated immune responses in a patient during ongoing infection and/or inflammation in said patient is disclosed.

ATTORNEY/DOCKET NO: **LIGN3005/REF**

DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention (Design, if applicable) entitled:

USE OF XANTHOPHYLLS, ASTAXANTHIN E.G., FOR TREATMENT OF AUTOIMMUNE DISEASES, CHRONIC VIRAL AND INTRACELLULAR BACTERIAL INFECTIONS

the specification of which (check one):

☐ is attached hereto, or ☒ was filed on: **5 October 2000** as PCT International Application Number: **PCT/SE00/01923**

and (if applicable) was amended on:

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in *Title 37, Code of Federal Regulations, §1.56.* I hereby claim foreign priority benefits under *Title 35, United States Code §119* of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			PRIORITY CLAIMED	
Number	Country	Day/Month/Year Filed	Yes	No
9903619-6	Sweden	5 October 2000	X	

☐ Additional Priority Application(s) Listed on Following Page(s)

I HEREBY CLAIM THE BENEFIT UNDER TITLE 35 U.S. CODE §119(E) OF ANY U.S. PROVISIONAL APPLICATIONS LISTED BELOW.	
Application Number	Day/Month/Year Filed

☐ Additional Provisional Application(s) Listed on Following Page(s)

I hereby claim the benefit under *Title 35, United States Code, §120* of any United States application(s) or PCT international application(s) designating The United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of *Title 35, United States Code, §112*, I acknowledge the duty to disclose information which is material to patentability as defined in *Title 37, Code of Federal Regulations, §1.56* which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Application Number	Filing Date	Status - Patented, Pending or Abandoned

☐ Additional US/PCT Priority Application(s) listed on Following Page(s)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under *section 1001 of title 18 of the United States Code* and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I (We) hereby appoint as my (our) attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: J. Ernest Kenney, Reg. No. 19,179; Eugene Mar, Reg. No. 25,893; Richard E. Fichter, Reg. No. 26,382; Thomas J. Moore, Reg. No. 28,974; Joseph DeBenedictis, Reg. No. 28,502; Benjamin E. Urcia, Reg. No. 33,805; and

(6)

I(we) authorize my(our) attorneys to accept and follow instructions from Stockholms Patentbyra Zacco AB regarding any matter related to the preparation, examination, grant and maintenance of this application, any continuation, continuation-in-part or divisional based thereon, and any patent resulting therefrom, until I(we) or my(our) assigns withdraw this authorization in writing.

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☒ *See following page(s) for additional joint inventors.*

(04A(0)1998)

ATTORNEY/DOCKET NO: LIGN3005/REF

CONTINUATION OF DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

2-00

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DATE	SIGNATURE

☐ *See following pages for additional joint inventors/priority applications.*

(04AUG1998)